PCT/EP2004/007241

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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Dated 21 April 2004

Patents Form 1/77

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Request for grant of a patent

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1.	Your reference	4-33159P1
2.	Patent application number *(The Patent Office will fill in this)*	0315654.4
		04JUL03 E820094-3 D00245 P01/7700 0.00-0315654.4 03 JUL 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	7181522002

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	Yes
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	12
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

3rd July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr 01403 323069

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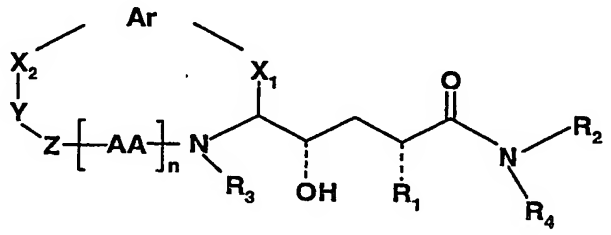
DUPLICATE

Organic Compounds

The present invention relates to novel macrocyclic compounds, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides compounds of formula I



I

wherein

R_1 is (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, hydroxy(C_{1-6})alkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, (C_{1-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, piperidinyl or pyrrolidinyl,

R_2 and R_4, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7}) cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4}) alkyl, or

R_2 and R_4, together with the nitrogen to which they are attached, form an optionally substituted piperidino, pyrrolidinyl, morpholino or piperazinyl group,

R_3 is hydrogen or (C_{1-4})alkyl,

X_1 is CH_2,

X_2 is CH_2, O, S, CO, COO, OCO, NHCO, CONH, or NR, R being hydrogen or (C_{1-4})alkyl,

Y is (C_{1-8})alkylen or (C_{1-8})alkylenoxy(C_{1-6})alkylen, (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy (C_{1-6})alkylen,

Ar is a phenyl ring optionally mono- di- or trisubstituted by, independently, hydroxy or halogen, whereby X_1 and X_2 are in meta or para position to each other,

and either

Z is CO,

AA is a natural or unnatural alpha-amino-acid, and

n is 0 or 1,

or

Z is SO_2,

AA is an optionally substituted ethylencarbonyl group (derived from a natural or unnatural alpha-amino acid by replacement of the nitrogen by a methylen group), and

n is 1

in free base or acid addition salt form.

Halogen denotes fluorine, bromine, chlorine or iodine.

When R_2 and/or R_4 is substituted alkyl or cycloalkyl, or together with the nitrogen to which they are attached, form a substituted piperidino, pyrrolidinyl, morpholino or piperazinyl group, substituents may be one to three groups selected from hydroxy, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkoxy, (C_{1-4})alkylsulfanyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonylamino, (C_{1-4})alkylcarbonyl, (C_{1-4})sulfonyl, cyano, oxo, hetero (C_{3-7})cycloalkyl or heteroaryl.

When R_2 and/or R_4 is substituted aryl or heteroaryl, substituents may be one to three groups selected from halogen, hydroxy, cyano, trifluoromethyl, carboxy, (C_{1-4})alkyloxycarbonyl, (C_{1-4})alkylcarbamoyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, (C_{1-4})alkyl, (C_{1-4})alkoxy or hydroxy(C_{1-4})alkyl.

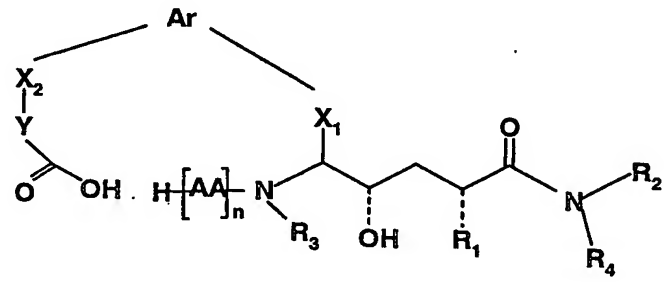
Aryl is an aromatic 6-membered ring optionally mono-, di- or tri-substitueted by, independently, hydroxy, cyano, trifluoromethyl, carboxy, (C_{1-4})alkyloxycarbonyl, (C_{1-4})alkylcarbamoyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonylamino, (C_{1-4})alkylcarbonyl, (C_{1-4})alkyl, (C_{1-4})alkoxy or hydroxy(C_{1-4})alkyl. It can also be fused with an cycloalkyl or additional aromatic or heteroaromatic ring (e.g. to form a naphthyl, quinolinyl, indolyl group).

Heteroaryl is an aromatic 5- or 6- membered ring in which 1, 2 or 3 atoms are heteroatoms independently selected from O, N and S, optionally mono- di- or tri- substituted by, independently, hydroxy or halogen. Heteroaryl is for example 1-methyl-1H-pyrrol-2-yl or 1H-imidazol-2-yl. It can also be fused with an cycloalkyl or additional aromatic or heteroaromatic ring (e.g. to form a quinolinyl, indolyl group).

Any alkyl or alkoxy group is straight or branched and is preferably methyl or methoxy.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the steps of

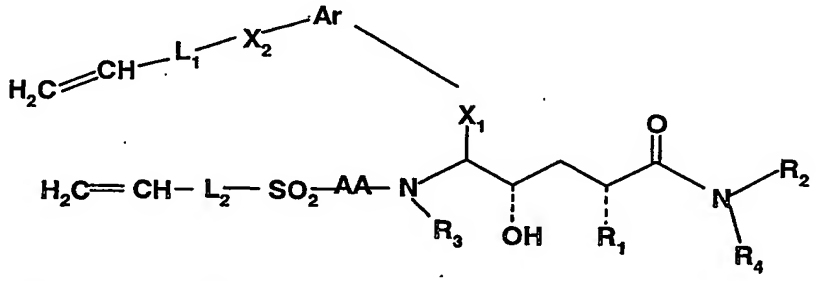
a) for the production of a compound of formula I wherein Z is CO, cyclisation by amide formation of a compound of formula II



II

wherein R_1, R_2, R_3, R_4, X_1, X_2, Y, Ar, AA and n are as defined above,

b) for the production of a compound of formula I wherein Z is SO_2 and Y is (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen, cyclisation by metathesis of a compound of formula III.



III

wherein R_1, R_2, R_3, R_4, X_1, X_2, Ar and AA are as defined above and L_1 and L_2, independently are alkylen or alkylenoxyalkylen groups, or

c) for the production of a compound of formula I wherein Z is SO_2 and Y is (C_{1-8}) alkylen or (C_{1-8})alkylenoxy(C_{1-6})alkylen, hydrogenation of a compound of formula I wherein Z is SO_2 and Y is
(C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen,

and recovering the so obtained compound of formula I in free base or acid addition salt form.

The reactions can be effected according to known methods, for example the cyclisation of process A can be effected as described in Example 1.

Working-up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

The starting material of formula II may be produced for example as described in Example 1.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

The agents of the invention are inhibitors of aspartic proteases and can be used for the treatment of disorders involving processing by such enzymes. Particularly they inhibit beta-secretase and as such inhibit the generation of beta-amyloid and the subsequent aggregation into oligomers and fibrils.

Test 1 Inhibition of BACE

Recombinant BACE (extracellular domain, expressed in baculovirus and purified using standard methods) at 6 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM acetate buffer, pH 4.5, containing 0.1 % CHAPS. Synthetic peptide substrate Mca-Ser-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-Lys(DNP) is added to a final concentration of 3 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of BACE-activity as a function of test compound concentration.

Test 2 Inhibition of BACE-2

Recombinant BACE-2 (extracellular domain, expressed in baculovirus and purified using standard methods) at 2.5 nM concentrationis incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM acetate buffer, pH 4.5, containing 0.1 % CHAPS. Synthetic peptide substrate Mca-Ser-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-

Lys(DNP) is added to a final concentration of 3 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of BACE-2-activity as a function of test compound concentration.

Test 3 Inhibition of Cathepsin D

Recombinant cathepsin D (expressed as procathepsin D in baculovirus, purified using standard methods and activated by incubation in sodium formate buffer pH 3.7) is incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM sodium formate buffer, pH 3.1. Synthetic peptide substrate Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(DNP)-D-Arg-NH_2 is added to a final concentration of 2 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of cathepsin D-activity as a function of test compound concentration.

Test 4 Inhibition of cellular release of amyloid peptide 1-40

Chinese hamster ovary cells are transfected with the gene for amyloid precursor protein. Cells are plated at a density of 8000 cells/well in a 96- well microtiter plate and cultivated for 24 hours in DMEM cell culture medium containing 10 % FCS. Test compound is added to the cells at various concentrations, and cells are cultivated for 24 hours in presence of test compound. Supernatants are collected, and concentration of amyloid peptide 1-40 is determined using sandwich ELISA. Potency of the compound is calculated from the percentage of inhibition of amyloid peptide release as a function of test compound concentration.

Test 5 Cytotoxicity

Cytotoxicity of test compound is determined using Chinese hamster ovary cells transfected with the gene for amyloid precursor protein. Cells are plated at a density of 8000 cells/well in a 96- well microtiter plate and cultivated for 24 hours in DMEM cell culture medium containing 10 % FCS. Test compound is added to the cells at various concentrations, and cells are cultivated for 24 hours in presence of test compound. After removing the supernatant, the percentage of living and dead cells is determined using a colorimetric readout (MTS-method), which measures mitochondrial dehydrogenase enzymes in living cells.

The agents of the invention are therefore useful e.g. for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral haemorrhage with amyloidosis.

Some of the agents of the invention also inhibit BACE2 (beta-site APP-cleaving enzyme 2) or Cathepsin D, close homologues of beta-secretase. Due to the correlation of BACE2 and CathD expression with a more tumorigenic and metastatic potential of tumor cells, such inhibitors are useful for the suppression of the metastasis process associated with tumor cells.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 10 to about 2000, preferably from about 10 to about 200 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for

example, from about 1 to about 1000, preferably from about 1 to about 500 mg of an agent of the invention.

The agents of the invention can be administered alone or in combination with other pharmaceutical agents effective, in the treatment of conditions mentioned above.

The pharmaceutical combination may be in form of a unit dosage form, whereby each unit dosage will comprise a predetermined amount of the two components, in admixture with suitable pharmaceutical carriers or diluents. Alternatively, the combination may be in form of a package containing the two components separately, e.g. a pack or dispenser-device adapted for the concomitant or separate administration of the two active agents, wherein these agents are separately arranged.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

In still a further aspect the present invention provides a method for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

General abbreviations:

BOC	tert-butoxycarbonyl
BOP	benotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
DMPU	N, N'-dimethylpropyleneurea
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
EtOAc	ethylacetate
h	hours
HOBt	hydroxybenztriazole
HPLC	high pressure liquide chromatography
min	minutes

MS	mass spectroscopy
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example 1: (2R,4S)-N-Butyl-4-hydroxy-4-((13S,16S)-21-hydroxy-13-methyl-11,14-dioxo-9-oxa-12,15-diaza-tricyclo[16.3.1.0*3,8*]docosa-1(21),3,5,7,18(22),19-hexaen-16-yl)-2-methyl-butyramide

a) [1-Benzenesulfonyl-2-(3-benzyloxy-phenyl)-ethyl]-carbamic acid tert-butyl ester

A suspension of (3-Benzyloxy-phenyl)-acetaldehyde (20.6g, 91mmol), tert-butylcarbamate (10.7g, 91mmol, 1eq), sodium benzenesulfinate (18.3g, 109mmol, 1.2eq) and formic acid (5.2ml, .137mmol, 1.5eq) in 155 ml acetonitrile is stirred at 80°C for 4 h. After cooling to rt the mixture is taken up in EtOAc. The solution is washed with bicarbonate and brine, dried over magnesium sulfate and evaporated. The residue (37.3g) is used for the next step without further purification.
MS (LC/MS): 490 (M+Na)

b) [(S*)-2-(3-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

5H-Furan-2-one (11.2ml, 160mmol, 2eq) in THF (60ml) is added slowly to a solution of lithium diisopropylamide (80ml commercial 2M solution in THF/heptane/ethylbenzene, 160mmol, 2eq) in THF (180ml) at -78°C. The mixture is stirred for another 20min at -78°C before [1-Benzenesulfonyl-2-(4-benzyloxy-phenyl)-ethyl]-carbamic acid tert-butyl ester (37.3g, 80mmol) in THF (220ml) is added at the same temperature. After stirring for another 45 min at -78°C aqueous bicarbonate solution is added and the reaction mixture is taken up into EtOAc. The organic layer is washed with bicarbonate and brine and dried over magnesium sulfate. Evaporation of the solvent gives a residue that is purified by chromatography on silica using hexan/EtOAc 9/1 to 7/3. The product is recrystallized from ether/hexane to give the product as white crystals (11.1g)
MS (LC/MS): 432 (M+Na)

1H-NMR (400MHz, CDCl3): 7.45-7.2 (m, 7H), 6.9-6.85 (m, 3H), 6.06 (d, 1H), 5.07 (s, 2H), 4.90 (d, 1H), 4.50 (d, 1H), 4.20 (q, 1H), 3.01 (dd, 1H), 2.91 (dd, 1H), 1.38 (s, 9H).

c) [(S*)-2-(3-Benzyloxy-phenyl)-1-((S*)-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

[(S*)-2-(4-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (11.1g, 27mmol) is hydrogenated (1atm H_2) at rt in THF (550ml) with Pt/C as catalyst (5% Engelhard 4709, 2.3g) during 1h. The catalyst is filtered off and the filtrate is evaporated. Purification by chromatography on silica (Flashmaster, hexane to hexane/EtOAc 55/45 over 40min) gives the product as yellowish oil (10.4g).
MS (LC/MS): 434 (M+Na)
1H-NMR (400MHz, CDCl3): 7.45-7.2 (m, 6H), 6.9-6.8 (m, 3H), 5.06 (s, 2H), 4.61 (d, 1H), 4.44 (t, 1H). 4.00 (q, 1H), 2.95 (dd, 1H), 2.85 (dd, 1H), 2.6-2.45 (m, 2H), 2.15-2.1 (m, 2H), 1.42 (s, 9H).

d) [(S*)-2-(3-Benzyloxy-phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

To a solution of [(S*)-2-(4-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (11.4g, 27.7mmol) in THF (35ml) and DMPU (5ml, 42mmol, 1.5eq) at -78°C is added dropwise lithium-bis-(trimethylsilyl)-amide (55ml 1M solution in THF, 55mmol, 2eq). After stirring at -78°C for another 45 min methyliodide is added dropwise and the mixture is stirred another 3h at -78°C. Propionic acid (10.3 ml, 138mmol, 5eq) is added followed by water (10ml). After warming up to 0°C a 10% solution of citric acid (72ml) is added. The reaction mixture is extracted with EtOAc. The organic layer is washed with bicarbonate, 0.1N sodium sulfite and brine, dried over magnesium sulfate and evaporated. Purification by chromatography on silica (hexane/EtOAc 9/1 to 4/1) followed by recrystallization from ether/hexane gives white crystals (8.14g).
MS (LC/MS): 448 (M+Na)
1H-NMR (400MHz, CDCl3): 7.45-7.2 (m, 6H), 6.9-6.8 (m, 3H), 5.05 (s, 2H), 4.53 (d, 1H), 4.45 (t, 1H), 4.00 (q, 1H), 2.93-2.85 (m, 2H), 2.74-2.68 (m, 1H), 2.41-2.34 (m, 1H), 1.89-1.82 (m, 1H), 1.41 (s, 9H), 1.26 (d, 3H).

e) [(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-carbamic acid tert-butyl ester

[(S*)-2-(3-Benzyloxy-phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (4.0g, 9.4mmol) is dissolved in butylamine (200ml) and stirred for 18 h in an heating bath of 90°C. The butylamine is evaporated and the residue is recrystallized from dichloromethane/ether/hexane to give white crystals (4.42g).
MS (LC/MS): 521 (M+Na)
1H-NMR (400MHz, CDCl3): 7.45-7.15 (m, 6H), 6.9-6.8 (m, 3H), 5.91 (s, 1H), 5.04 (s, 2H), 4.89 (d, 1H), 3.7-3.6 (m, 2H), 3.3-3.1 (m, 2H), 2.9-2.85 (m, 2H), 2.6-2.5 (m, 1H), 1.75-1.6 (m, 2H), 1.5-1.25 (m, 4H), 1.41 (s, 9H), 1.12 (d, 3H), 0.92 (t, 3H).

f) {(S)-1-[(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester

[(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-carbamic acid tert-butyl ester (4.4g, 8.8mmol) is dissolved in trifluoroacetic acid (95ml) and stirred at rt during 1.25h. The solvent is evaporated and the residue is a few times redissolved in ether and dried again to give a white foam (3.92g, 9.0mmol). The foam is dissolved in dichloromethane (210ml) and BOC-L-alanine (1.05g, 10.8mmol, 1.2eq), EDCI (2.59g, 13.5mmol, 1.5eq), HOBt (1.46g, 10.8mmol, 1.2eq) and triethylamine (3.76g, 27mmol, 3eq) are added. The reaction is stirred at rt (with an argon balloon) for 18 h. The mixture is extracted with EtOAc and the organic layer is washed with 0.5N HCl, brine, bicarbonate and brine again, and dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from dichloromethane/ether/hexane gives the product as an about 1/1 mixture of diastereomers (4.45g).
MS (LC/MS): 593 (M+Na)
1H-NMR (400MHz, CDCl3): 7.45-7.15 (m, 6H), 6.9-6.8 (m, 3H), 6.47/6.30 (d, 1H), 5.90 (s, 1H), 5.08 (s, 2H), 5.0-4.85 (m, 1H), 4.1-3.98 (m, 2H), 3.77-3.70 (m, 1H), 3.3-3.15 (m, 2H), 2.95-2.85 (m, 2H), 2.6-2.5 (m, 1H), 1.8-1.55 (m, 3H), 1.5-1.4 (m, 10H), 1.4-1.3 (m, 2H), 1.26/1.20 (d, 3H), 1.12-1.08 (m, 3H), 0.95-0.9 (m, 3H).

g) {(S)-1-[(1S*,2S*,4R*)-4-Butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester

{(S)-1-[(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester (4.44g, 7.8mmol) is hydrogenated at rt (1 atm H_2) in ethanol (240ml) with Pd/C (10% Engelhard 4505, 0.69g) for 4h. The catalyst is filtered off and the filtrate is evaporated to give a white foam (3.76g, about 1/1 mixture of diastereomers).
MS (LC/MS): 502 (M+Na)
1H-NMR (400MHz, CDCl3): 7.14 (t, 1H), 6.78-6.7 (m, 3H), 6.65/6.55 (d, 1H), 6.25/6.08 (s, 1H), 5.26/5.08 (d, 1H), 4.15-3.95 (m, 2H), 3.75-3.7 (m, 1H), 3.3-3.15 (m, 2H), 2.93-2.8 (m, 2H), 2.65-2.52 (m, 1H), 2.0-1.5 (m, 5H), 1.5-1.4 (m, 10H), 1.4-1.3 (m, 2H), 1.30/1.25 (d, 3H), 1.15-1.10 (m, 3H), 0.94 (t, 3H).

h) 6-{3-[(2S*,3S*,5R*)-2-((S)-2-tert-Butoxycarbonylamino-propionylamino)-5-butylcarbamoyl-3-hydroxy-hexyl]-phenoxy}-hexanoic acid tert-butyl ester

{(S)-1-[(1S*,2S*,4R*)-4-Butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester (1.20g, 2.5mmol) is dissolved in acetone (250ml) and treated with 6-Bromo-hexanoic acid tert-butyl ester (CAS 65868-63-5, 0.94g, 3.8mmol, 1.5eq), water free potassium carbonate (1.04g, 7.5mmol, 3eq) and potassium iodide (0.42g, 2.5mmol, 1eq). The mixture is heated at reflux temperature (bath temperature 75°C) for 5 days. The reaction mixture is diluted with EtOAc, washed with brine, dried over magnesium sulfate and evaporated. The crude product is purified by chromatography on silica (flashmaster, dichloromethane to dichloromethane/MeOH 90/10; mixed fractions are collected and resubmitted to chromatography). After a total of 5 chromatographies and recrystallization from ether/hexane white crystals are obtained (1.28g, about 1/1 mixture of diastereomers).
MS (LC/MS): 672 (M+Na)
1H-NMR (400MHz, C2D2Cl4): 7.25 (t, 1H), 6.88-6.82 (m, 3H), 6.32/6.20 (d, 1H), 5.33/5.17 (s, 1H), 4.43/4.33 (d, 1H), 4.15-4.03 (m, 4H), 3.82 (s, 1H), 3.45-3.2 (m, 3H), 3.03-2.90 (m, 2H), 2.60-2.53 (m, 1H), 2.33 (t, 2H), 1.90-1.80 (m, 2H), 1.80-1.65 (m, 3H), 1.65-1.4 (m, 25H), 1.35/1.32 (d, 3H), 1.19 (d, 3H), 1.03 (t, 3H).

i) (S)-1-{(1S,2S,4R)-4-Butylcarbamoyl-1-[3-(5-carboxy-pentyloxy)-benzyl]-2-hydroxy-pentylcarbamoyl}-ethyl-ammonium trifluoroacetate

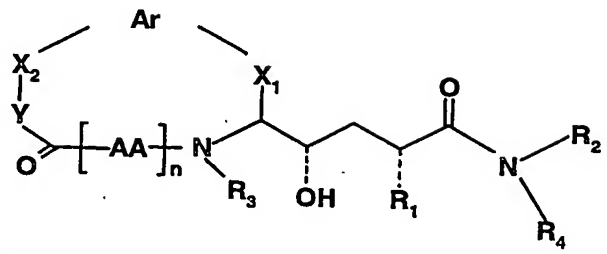
6-{3-[(2S*,3S*,5R*)-2-((S)-2-tert-Butoxycarbonylamino-propionylamino)-5-butylcarbamoyl-3-hydroxy-hexyl]-phenoxy}-hexanoic acid tert-butyl ester (1.25g, 1.9mmol) is dissolved in trifluoroacetic acid (40ml) and water (4.5ml) at 0°C and stirred for 30min. The reaction mixture is diluted with 380ml cold water and the solvents are evaporated at rt. The two enantiomerically pure diastereomers are separated by preparative HPLC (Nucleosil 100-5 C18, water/acetonitrile 90/10 to acetonitrile). The first diastereomer is collected in about 80% purity and used directly for the next step (0.26g).
MS (LC/MS): 516 (M+Na)

j) (2R,4S)-N-Butyl-4-hydroxy-2-methyl-4-((10S,13S)-10-methyl-8,11-dioxo-2-oxa-9,12-diaza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-13-yl)-butyramide

(S)-1-{(1S,2S,4R)-4-Butylcarbamoyl-1-[3-(5-carboxy-pentyloxy)-benzyl]-2-hydroxy-pentylcarbamoyl}-ethyl-ammonium trifluoroacetate (0.26g, 4.3mmol) is dissolved in DMF (60ml) and BOP (0.28g, 6.4mmol, 1.5eq) and diisopropylethylamine (0.47ml, 27.8mmol, 6.5eq) are added. The reaction mixture is stirred over night at rt. The solvent is evaporated at rt and the residue is taken into EtOAc. Washing with 0.5N HCl, brine, bicarbonate and brine again, drying over magnesium sulfate and evaporation of the solvent gives the crude product. This is purified by preparative HPLC (Nucleosil 100-5 C18, water/acetonitrile 90/10 to acetonitrile) to give the title compound as white powder after liophilisation (26mg).
MS (LC/MS): 498 (M+Na)
1H-NMR (400MHz, CD3OD): 7.15 (t, 1H), 6.8-6.7 (m, 3H), 4.53 (q, 1H), 4.15-4.05 (m, 2H), 4.05 (d, 1H), 3.60 (dt, 1H), 3.18 (t, 2H), 2.86 (d, 1H), 2.73-2.6 (m, 2H), 2.27-2.22 (m, 1H), 2.16-2.10 (m, 1H), 1.84-1.65 (m, 4H), 1.55-1.3 (m, 8H), 1.27 (d, 3H), 1.17 (d, 3H), 0.95 (t, 3H).

Claims:

1. A compound of formula I



I

wherein

R_1 is (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, hydroxy(C_{1-6})alkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, (C_{1-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, piperidinyl or pyrrolidinyl,

R_2 and R_4, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7}) cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4}) alkyl, or

R_2 and R_4, together with the nitrogen to which they are attached, form an optionally substituted piperidino, pyrrolidinyl, morpholino or piperazinyl group,

R_3 is hydrogen or (C_{1-4})alkyl,

X_1 is CH_2,

X_2 is CH_2, O, S, CO, COO, OCO, NHCO, CONH, or NR, R being hydrogen or (C_{1-4})alkyl,

Y is (C_{1-8})alkylen or (C_{1-8})alkylenoxy(C_{1-6})alkylen, (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen,

Ar is a phenyl ring optionally mono- di- or trisubstituted by, independently, hydroxy or halogen, whereby X_1 and X_2 are in meta or para position to each other,

and either

Z is CO,

AA is a natural or unnatural alpha-amino-acid, and

n is 0 or 1,

or

Z is SO_2,

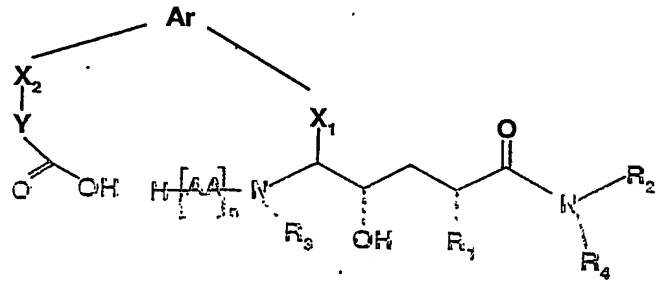
AA is an optionally substituted ethylencarbonyl group (derived from a natural or unnatural alpha-amino acid by replacement of the nitrogen by a methylen group), and

n is 1

in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which includes the steps of

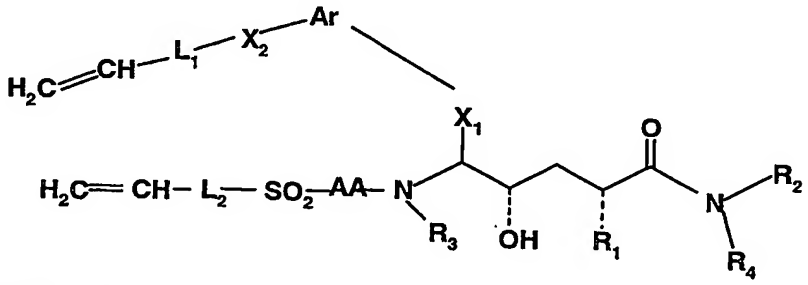
a) for the production of a compound of formula I wherein Z is CO, cyclisation by amide formation of a compound of formula II



II

wherein R_1, R_2, R_3, R_4, X_1, X_2, Y, Ar, AA and n are as defined in claim 1,

b) for the production of a compound of formula I wherein Z is SO_2 and Y is (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen, cyclisation by metathesis of a compound of formula III



III

wherein R_1, R_2, R_3, R_4, X_1, X_2, Ar and AA are as defined in claim I and L_1 and L_2, independently are alkylen or alkylenoxyalkylen groups, or

c) for the production of a compound of formula I wherein Z is SO_2 and Y is (C_{1-8}) alkylen or (C_{1-8})alkylenoxy(C_{1-6})alkylen, hydrogenation of a compound of formula I wherein Z is SO_2 and Y is (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen,

and recovering the so obtained compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

5. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical, for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

8. A method for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound of claim 1 in free base of pharmaceutically acceptable acid addition salt form and a second drug substance, for simultaneous or sequential administration.